Nocturia
Overview

- Epidemiology
- Pathophysiology
- Evaluation and Diagnosis
- Treatments
  - General
  - Nocturnal Polyuria
  - BPH
  - OAB
- Conclusion
**Definition**

- **Nocturia** is “the complaint that the individual has to wake at night 1 or more times to void”

- Important to establish whether the individual has awoken at night to void, or voids because he or she is already awake.
Epidemiology
Prevalence

Review of 43 studies

Bosch, R. "The prevalence and Causes of Nocturia" The Journal of Urology, 184;440-446, 2010
Number of Nocturia Episodes

Ruud Bosch et al, The Journal of Urology, 2010;184;440-446
Prevalence – Epic Study

- n=19165 from Canada, Germany, Italy, Sweden and UK
- Overall ~ 50% of men and woman
- 35% of 40 year olds
- 50% of 50 year olds
- 70% of 60 year olds
- Nocturia most prevalent “LUTS”
- Bothersome and associated with a decrease QOL

On average, after falling asleep, how many times are you awakened at night with the need to urinate?

<table>
<thead>
<tr>
<th>Group, n (%)</th>
<th>Symptom Frequency</th>
<th>Nocturia ≥ 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>136 (13.6)</td>
<td>364 (36.4)</td>
</tr>
<tr>
<td>Men</td>
<td>59 (12.2)</td>
<td>160 (33.2)</td>
</tr>
<tr>
<td>Women</td>
<td>77 (14.9)</td>
<td>204 (39.4)</td>
</tr>
<tr>
<td>Age groups, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–40</td>
<td>17 (8.5)</td>
<td>47 (23.5)</td>
</tr>
<tr>
<td>41–64</td>
<td>35 (15.4)</td>
<td>92 (40.4)</td>
</tr>
<tr>
<td>≥65</td>
<td>7 (14.9)</td>
<td>21 (44.7)</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–40</td>
<td>33 (15.1)</td>
<td>66 (30.3)</td>
</tr>
<tr>
<td>41–64</td>
<td>31 (13.3)</td>
<td>107 (45.9)</td>
</tr>
<tr>
<td>≥65</td>
<td>13 (22.4)</td>
<td>31 (53.4)</td>
</tr>
<tr>
<td>All</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–40</td>
<td>50 (12.0)</td>
<td>113 (27.0)</td>
</tr>
<tr>
<td>41–64</td>
<td>66 (14.3)</td>
<td>199 (43.2)</td>
</tr>
<tr>
<td>≥65</td>
<td>20 (19)</td>
<td>52 (49.5)</td>
</tr>
</tbody>
</table>

Herschorn, Gajewski et al BJU International 2007
Overall, rate of nocturia is equal for men and woman.

- > 1 void/night
- > 2 voids/night

Impact on Health - Why we care

- Nocturia fragments sleep and has profound effects on overall health, well-being, and function. 1st hours sleep most restorative.
- Early on in sleep slow-wave pattern (restorative) occurs.
- A single nocturia impact on the patient may have greater impact if it occurs earlier in the nights sleep.

Impact on Health – Why we care

- QoL
- Mood
- Work absenteeism
- Daytime function
- Fractures
- Mortality
- Daytime sleepiness

Impact on Health - QoL

6000 sent questionnaire, AUA-SI., DPSS, 15D

547 male patients completed American Urological Association Symptom Score (AUA-SS) and Geriatric Depression Scale (GDS).

AUA- SI – incomplete emptying, frequency, intermittency, urgency, weak stream, straining, and nocturia.
GDS – short version with 15 questions. >10 = depression

Those with 5 or more episode nocturia experienced a 6.5 fold increase risk of depression.

Impact on Health - Depression

Johnson, et al, Urology, 77 (1), 2011
Impact on Health – Activity and work impairment

Fig. 3. Overall work and activity impairment in nocturic versus non-nocturic control men measured with the Work Productivity and Activity Impairment (WPAI) index [51].
Prospective Population based study.
Started with an intensive interview, then patients followed.
784 individuals (all > 70, mean age 76) followed for mean of 4.6 years.
Nocturia (2 or more) associated with HR 2.01 for fall related fractures and 1.98 for death.
(this adjusts for diabetes, smoking, CAD, renal and stroke)

J Urol. 2010 Oct;184(4):1413-8
Impact on Health - # and Mortality

Nakagawa et al. The Journal of Urology, 184, 1413-1418 (2010)
Pathophysiology
Causes of nocturia

- **Polyuria** - polydipsia, DM, DI, Drugs.
- **Nocturnal Polyuria** - circadian rhythm, CHF, renal impairment, hepatic failure, drugs, OSA
- **Diminished nocturnal bladder capacity** - incomplete voiding, detrusor overactivity, detrusor hypersensitivity, BOO (BPH, Bladder neck)
- **Sleep disorder**
- **Mixed**

48 children (28 OSA vs 20 controls) followed with respiratory indices, 12-hr urine volume, and ADH levels before and after adenotonsillectomy

Results:

Pathophysiology- Sleep Apnea

- 32 male and female patients mean age 65yrs with nocturia and ½ with OSA
- Sleep study, Blood and Urine
- Results:
  - Total Urine output, ANP(plasma and urine) WERE significantly higher among OSA, apneic, or hypoxic episodes
- Conclusion:
  - OSA with apneic episodes have higher nighttime urine production and elevated ANP excretion

Umlauf MG et al. Sleep. 2004
How does functional capacity and first sensation during cystometrogram relate to nocturia?

Table 3

<table>
<thead>
<tr>
<th>Level of Nocturia</th>
<th>Mean Maximum Cystometric Capacity (mLs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>350 ± 10</td>
</tr>
<tr>
<td>2</td>
<td>300 ± 10</td>
</tr>
<tr>
<td>3</td>
<td>250 ± 10</td>
</tr>
<tr>
<td>&gt;3</td>
<td>200 ± 10</td>
</tr>
</tbody>
</table>

p<0.0001
Weiss et al. looked at 845 pts (men and women) found:

1. nocturnal bladder capacity decreases with advancing age
2. nocturnal polyuria increased with advancing age
Danish study (Copenhagen) men and women age 60 to 80

75 patients who had H and P, FVC +/- Bladder Scan +/- UD

Bing MH et al. J Urology. 2007
## Causes of Nocturia- general

- “Nocturia: an Austrian study on the multifactorial etiology of this symptom”
- Excluded UTI’s and PVR>200

<table>
<thead>
<tr>
<th>Causes</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nocturnal Polyuria</td>
<td>33%</td>
</tr>
<tr>
<td>Global Polyuria</td>
<td>17%</td>
</tr>
<tr>
<td>Reduced Functional Capacity &lt;250 cc</td>
<td>16%</td>
</tr>
<tr>
<td>Mixed Forms of NP</td>
<td>21%</td>
</tr>
<tr>
<td>Other</td>
<td>12%</td>
</tr>
</tbody>
</table>

Pathophysiology- conclusions

- It is SYMPTOM of a general medical illness, less often urological.

- Different types of nocturia have different causes
  - Not the “failure to store, failure to empty”
  - Often “failure to store a massive flood”
Investigations
Investigations - Screen

- An initial screen should include a detailed history
- Questions relevant to voiding behaviour, medical and neurological abnormalities and sleep disturbance
- Information on relevant surgery or previous urinary infections
- A simple urine test, such as dipstick or urinalysis
- A physical exam
1. Voiding diary (24 hr, freq-vol)
2. Labs:
   - glucose (urine and blood), HBA1c, BNP/ANP
3. Review meds: diuretics, lithium, etc.
4. Others:
   - Albumin, Na intake, sleep study (OSA)
24 hour voiding diary and calculate:

1. How much urine per night (%) → NPi
   - Night volume divided by 24hr (total) volume
   - > 30 percent suggestive of nocturnal polyuria

2. How does volume produced at night compare to the max voided volume (capacity) → Ni
   - Could be because functional bladder capacity exceeded.
Global polyuria:
- >2.8L or >40cc/kg per 24 hours eg. 70 kg man urine volume >2800 cc (~3L/day or more is poluria)

Nocturnal Polyuria:
- >30% NPi (night volume divided by total volume)

Neither or Ni>1 eg. OAB, Mixed etc.
Investigations

New Wee Entry

Date: 2011-03-16 2:38 PM

- Amount Voided
- Amount of Leakage
- Associated Urgency
- Associated Stress
- Replaced Protection
- Infection

S. De, MD
Treatments
Lifestyle and behavioural changes
- Reduce fluid intake
- Reduce caffeine/alcohol intake
- Adjust meds (eg. diuretics, timing, etc.)
- Shorten sleep time

Reduce edema
- Compressive stockings
- Leg elevation before bedtime
- Evening walk/exercise

Optimize (CHF, OSA, etc.)
- As per family MD, specialist referral
Treatment – Lifestyle Modification

- Four lifestyle measures (reduced fluids, decreased hours in bed, moderate exercise, warm bed) n=56
  - Nocturia episodes 3.6 to 2.7
  - NUV 923 to 768 (no change in 24hr urine volume)

- Evening exercise, n=30
  - 30 minutes evening walk x 8 weeks decreased nocturia episodes from 3.3 to 1.9

Synthetic analogue of ADH (pituitary)
Used for diabetes insipidus and nocturnal enuresis for years
Increased osmolality, decreased urine volume
Multiple studies:
- Men, women, elderly short and long term
Effects:
- Increases time to first nocturnal void
- Decreases number of nocturnal voids
- Decreases volume and percentage of urine voided at night
Side effects: (Increase with age)
- HA, nausea, dizziness, hyponatremia

Nocturnal Polyuria – Desmopressin vs. placebo

- European randomized double blind study (n=127 after dose-titration period)
- Desmopressin vs. Placebo
Mean nocturnal voids decreased (39% vs. 15% with absolute difference of 0.84 p<0.0001)
Duration of first sleep prolonged by 108 vs. 41 minutes p<0.0001)
**Nocturnal Polyuria – Desmopressin + Furosemide vs. placebo**

- Double-blind placebo controlled study (n=82)
- Desmopressin + Furosemide vs. Placebo.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Furosemide and desmopressin (n=39)</th>
<th>Placebo (n=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nocturnal voids (n)</td>
<td>3.5±1.1</td>
<td>3.3±1.0</td>
</tr>
<tr>
<td>Nocturnal urine volume (ml)</td>
<td>919.6±222.1</td>
<td>871.6±216.0</td>
</tr>
<tr>
<td>NPI</td>
<td>0.46±0.07</td>
<td>0.43±0.07</td>
</tr>
</tbody>
</table>

**P-value**
- <0.01
- <0.01
- <0.01

**Also improved duration of first sleep by 70 min**

Prospective randomized double-blind placebo controlled trial of afternoon furosemide

Goal: early evening diuresis and decreased nocturnal voiding (frequency and volume)

43 men, significant benefit of 40 mg lasix (6 hrs prior to usual bedtime) over placebo

Outcome:

- Mean reduction in nighttime voids 0.5 episodes vs 0.0 for placebo (p=0.014)
- Mean increase in daytime urine production 365ml
- Safe and well tolerated

56 consecutive patients who had a TURP.
- No control
- Increased interval to first void
- Decrease in nocturia events 3.4 to 2.6

**Table 1. Nocturia Indexes before and after prostatectomy**

<table>
<thead>
<tr>
<th>Index</th>
<th>Preoperatively</th>
<th>Postoperatively</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nocturia events (n)</td>
<td>3.4 ± 1.2</td>
<td>2.6 ± 0.99</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HUS</td>
<td>1.83 ± 0.55</td>
<td>2.74 ± 0.64</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tlong</td>
<td>2.36 ± 0.64</td>
<td>2.91 ± 0.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>N-QOL score</td>
<td>24.1 ± 7</td>
<td>34.4 ± 7.5</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

HUS = hours of undisturbed sleep; Tlong = longest sleep interval between voids; N-QOL = nocturia quality-of-life questionnaire.

Margel D et al. Urology. 2007
Randomized trial 66 patients.
33 given 0.4 mg Tamsulosin OD
33 had TURP
IPSS and ICIQ-N and 72-hr frequency chart to look at # nocturnal awakening and hour undisturbed sleep (HUS).
Excluded pts (excessive fluid intake, DM/DI, CHF, UTI, OAB, diuretics, previous treatment for BPH.)

IPSS- Over the past month, how many times did you typically get up to urinate from the time you went to sleep till the time you woke up?
ICIQ-N- Evaluates frequency and nocturia

International Journal of Urology (2011);18,243-249
RESULTS:
- IPSS and ICIQ-N showed improvement at 3 and 12 months for Tamsulosin and TURP (more for TURP)
- Decrease in nocturnal awakenings (0.5 and 0.6 for Tamsulosin, 0.9 and 1.0 for TURP) at 3 and 12 months
- HUS increased by 0.5-0.6 hrs for both
“Changes in nocturia from medical treatment of benign prostatic hyperplasia: secondary analysis of the department of veterans affairs cooperative study trial”

- 788 of 1078 men who had 2 or more episodes of nocturia
- Compared terazosin, finasteride, combination and placebo at 1 year
- Terazosin > combination therapy > finasteride = placebo
“The effect of Doxazosin, Finasteride and Combination Therapy on Nocturia in Men with Benign Prostatic Hyperplasia”

Secondary analysis of 3047 men in Medical Therapy of Prostatic Symptoms trial (MTOPS) with LUTS/BPH.

### BPO – alpha blocker and 5 alpha-reductase inhibitors

#### Table 1: Mean voids (n > 1)

<table>
<thead>
<tr>
<th></th>
<th>1 year</th>
<th>4 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxazosin</td>
<td>0.54</td>
<td>0.53</td>
</tr>
<tr>
<td>Finasteride</td>
<td>0.40</td>
<td>0.42</td>
</tr>
<tr>
<td>Combination</td>
<td>0.58</td>
<td>0.55</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.35</td>
<td>0.38</td>
</tr>
</tbody>
</table>

1 year → Doxazosin and Combination > Finasteride > Placebo
4 years → Doxazosin > Placebo

#### Table 2: Mean voids (n > 2)

<table>
<thead>
<tr>
<th></th>
<th>1 year</th>
<th>4 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxazosin</td>
<td>0.54</td>
<td>0.53</td>
</tr>
<tr>
<td>Finasteride</td>
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</tr>
<tr>
<td>Combination</td>
<td>0.58</td>
<td>0.55</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.35</td>
<td>0.38</td>
</tr>
</tbody>
</table>

1 year → Doxazosin and Combination > Finasteride > Placebo
4 years → No statistical difference

BPO – alpha blocker and 5 alpha-reductase inhibitors

1 year

4 years

BPH- Photoselective vaporization

- 103 pts with 2 or more episodes of nocturia
- MEAN- age 69, IPSS 21, Nocturia 3/night
- Prospectively followed 1, 2, 6, 12 months

**Table 2.** Baseline values and changes in PVP outcome parameters according to the IPSS and FVC (total patients)

<table>
<thead>
<tr>
<th>No. of patients at follow-up</th>
<th>Baseline</th>
<th>1 month</th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>103</td>
<td>100</td>
<td>82</td>
<td>69</td>
<td>61</td>
<td></td>
</tr>
</tbody>
</table>

**IPSS**
- Nocturia: 3.0±1.0, 2.4±1.2*, 2.1±0.9*, 2.0±0.9*, 2.1±1.0*
- Storage symptom: 8.5±3.1, 7.3±3.4*, 5.7±2.7*, 4.5±2.4*, 5.1±3.2*
- QoL index: 4.4±1.1, 2.7±1.4*, 2.4±1.9*, 2.0±1.3*, 2.1±1.4*

**FVC**
- Nocturia: 2.5±0.8, 2.0±0.9*, 1.7±0.8*, 1.5±0.7*, 1.5±0.8*
- FBC: 327±124, 326±117, 324±86, 358±123*, 359±123*
- NBCI: 0.83±0.82, 0.54±0.65*, 0.41±0.67*, 0.34±0.50*, 0.34±0.54*
- NBCI > 1: 61.2, 46.8, 37.8, 35.8, 34.5

PVP: photoselective vaporization of the prostate, IPSS: International Prostate Symptom Score, FVC: frequency-volume chart, QoL: quality of life, FBC: functional bladder capacity, NBCI: nocturnal bladder capacity index, *p < 0.05: comparison between the baseline parameters and parameters obtained after PVP by use of the paired t-test

Lee CJ et al. Korean J Urology. 2010 48
“Nighttime dosing with Tolterodine reduces overactive bladder-related nocturnal micturitions in patients with overactive bladder and nocturia”

- 2 week placebo run-in period
- 12 week randomized controlled study of 850 patients.
- Tolterodine 4mg ER vs. placebo 4 hrs or less before bed.
- Pts had a mean # void 2.5 or greater.
- Each void was rated on 1-5 scale for urgency.

Urology. 2006 Apr;67(4):731-6
OAB-Anticholinergics

A. Nighttime

<table>
<thead>
<tr>
<th>Group</th>
<th>Median % Change</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>-19</td>
<td>0.1450</td>
</tr>
<tr>
<td>Non-OAB</td>
<td>-44</td>
<td>0.4148</td>
</tr>
<tr>
<td>OAB</td>
<td>-22</td>
<td>0.0086</td>
</tr>
<tr>
<td>Severe OAB</td>
<td>-43</td>
<td>0.0221</td>
</tr>
</tbody>
</table>

Urgency Scale/5

1-2  3-5  4-5

Urology. 2006 Apr;67(4):731-6
“Clinical efficacy, safety and tolerability of once-daily Fesoterodine in subjects with overactive bladder”
12 week double blind placebo controlled multi center study (150 sites in 19 countries).
### Placebo TOL ER 4mg FESO 4mg FESO 8mg

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>TOL ER 4mg</th>
<th>FESO 4mg</th>
<th>FESO 8mg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nocturnal micturitions/24 h</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>n</em>‡</td>
<td>279 (254)</td>
<td>283 (266)</td>
<td>265 (247)</td>
<td>276 (255)</td>
</tr>
<tr>
<td>Baseline mean (SD)</td>
<td>1.8 (1.2)</td>
<td>2.0 (1.2)</td>
<td>1.9 (1.3)</td>
<td>2.0 (1.6)</td>
</tr>
<tr>
<td>LS mean (SE) change</td>
<td>−0.32 (0.06)</td>
<td>−0.40 (0.06)</td>
<td>−0.39 (0.06)</td>
<td>−0.39 (0.06)</td>
</tr>
<tr>
<td><em>p</em> value</td>
<td>0.336</td>
<td>0.394</td>
<td>0.418</td>
<td></td>
</tr>
<tr>
<td><strong>Median % change</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>−26.8</td>
<td>−25.0</td>
<td>−28.6</td>
<td>−23.1</td>
</tr>
<tr>
<td><em>p</em> value**</td>
<td>0.815</td>
<td>0.982</td>
<td>0.896</td>
<td></td>
</tr>
</tbody>
</table>
Blocks acetylcholine and induces selective and reversible muscle weakness.

Twenty-four patients (16 NDO, 8 IDO) treated with 300 mu BOTOX® (NDO) or 200 mu (IDO)

Completed a 4-d voiding diary before and 4 wk after treatment and a 7-d diary starting the day immediately after injections.
Nocturia is an important issue to address but a very hard symptom to treat.
Need to identify etiology of nocturia.
→ Voiding diary essential.
Treatments:
1) Lifestyle and behavior modification
2) TURP
3) Meds- DDAVP, diuretics, alpha-blockers, 5ARI’s, anticholinergics
4) Greenlight, botox
## Summary

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Decrease in # voids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifestyle</td>
<td>0.9-1.4*</td>
</tr>
<tr>
<td>TURP</td>
<td>0.8-1.0</td>
</tr>
<tr>
<td>Greenlight</td>
<td>1.0*</td>
</tr>
<tr>
<td>Desmopressin +/- Lasix</td>
<td>0.87-1.5</td>
</tr>
<tr>
<td>Lasix</td>
<td>0.5</td>
</tr>
<tr>
<td>Alpha-blocker</td>
<td>0.6-0.7</td>
</tr>
<tr>
<td>Anticholinergic</td>
<td>0-0.4</td>
</tr>
<tr>
<td>Botox</td>
<td>1.0*</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.3-0.4</td>
</tr>
</tbody>
</table>

(Studies all use different definitions; *not all randomized or placebo controlled)
The End

- Questions?